Application No.	Applicant(s)
09/707,468	NICOLAIDES ET AL

Office Action Summary

Examiner	Art Unit
Dave Nguyen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *5-8,12-21,26-28 and 30-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9-11,22-25 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,7-11,13*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Applicant's election with traverse of Group I claims, claims 1-4, 9-11, 22-25, and 29) in the response filed April 16, 2002 is acknowledged.

The traversal is that in view of Section 803.04, the restriction of six mismatch repair genes is not proper, that undue burden has not been established, the traversal is not found persuasive because section 803.04 only states that "up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction". Such statement does not indicate *per se* that an application claiming 6 mismatch repair genes ca not be restricted. Further, due to limited resources of the USPTO in searching sequences embraced by an already enormous breadth of each of genes as generically claimed, and due to an enormous number of claimed invention and the extent of the breadth of the claims, an undue burden has been established by the examiner if proper searches and considerations of multiple inventions have to be done for this application.

Applicant further traverses on page 3 that a common utility such as a determination of an effect on antibody production is sufficient for not to restrict the claims from the Groups set forth in the restriction, the traversal is not found persuasive because it is not apparent how a search of distinct materials and method steps set forth in each of the group claims whether or not the groups are involved in a common utility are related and/or overlapped with one another. With respect to citing same class and subclass, the fact that multiple distinct inventions are directed to same classes and/or subclasses do not establish applicant's assertion that there will be no serious burden on the examiner for examination of the claims as pending, especially when considering the nature of the each of the inventions and its intended breadth of the respective claims. With respect to the traversal of separating claims 36-41 into two groups (page 3, last full paragraph), the comments are not found persuasive because claims are read as broadly as possible when read in light of applicant's disclosure, and as such, the claims absent the limitation of *in vitro* and/or *in vivo* are properly restrictable. Applicant further argue that the claims do not set forth specific sequences and thus, the claims cannot be restricted, the comments are not found persuasive because not only the claims are attempted to claim an enormous number of sequences including SEQ identifiers for each of the six genes, the fact that the claims do embrace a SEQ identifier when read in light of the application, and as

such, the claims are properly restricted.

Claims 5-8, 12-21, 26-28, and 30-72 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Claims 1-4, 9-11, 22-25 and 29, readable on the elected claimed invention are pending for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 9-11, 22-25 readable on a genus of polynucleotide sequences of **a dominant negative allele** of a mismatch repair gene, which includes a subgenus of animal and/or mammalian genes coding for any dominant negative allele of a mismatch repair gene, and a further subgenus of PMS2 genes other than human PMS2 genes are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In addition, the claims readable on a method of making a generic **hypermutant transgenic animal including those of humans,** said animal comprising a cell whose genome in which any generic gene of dominant negative allele of a mismatch repair gene has been introduced are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The application contemplates that any dominant negative allele of mismatch repair (MMR) gene can be obtained from the cells of humans, animals, yeast, bacterial, or other organisms by screening

assays (page 9) and/or by synthetic assays. The as-filed application further contemplates that these polynucleotide sequences can be used to create any colony of hypermutable ransgenic animals including those of humans. The as-filed application coupled with the cited prior art provides sufficient description of homologs or native cDNA sequences, *e.g.*, SEQ ID NOS: 6, 8, 10, 12, and 14, belonging to a respective subgenus of mouse PMS2, human PMS2, human PMS1, human MSH2, and human MLH1. The as-filed application also incorporates a number of prior art, which mainly discloses that disruption of any native MMR gene including human PMS2 or murine PMS2 cause tumor and/or cancer. However and with respect to a genus of allelic variants of MMR genes which must exhibit the property of being dominant negative, *e.g.*, functional and being dominant over wild-typed MMR genes so as to cause hypermutation in a cell transfected with the variant, the application coupled with the cited prior art only provides description the human *hPMS2-134,* which carries a truncation mutation at codon 134, and encodes a dominant negative function over that of wild-typed hPMS2. However, neither the application nor the incorporated references provide structural description of a representative number of species of animal and/or mammalian native cDNA of allelic dominant negative PMS2 genes, let alone a representative number of species of naturally occurring **dominant negative alleles of MMR and/or PMS2 genes, and claims readable on** a method of making a generic hypermutant transgenic animal including those of humans, said animal comprising a cell whose genome in which any generic gene of dominant negative allele of a mismatch repair gene has been introduced. The claimed invention encompasses an enormous number of nucleic acid sequences encoding a dominant negative MMR genes including those of PMS2 other than mouse and human, and transgenic animal containing the sequences, wherein neither their sequence structure nor their biological activities have not been demonstrated. The claimed invention of the "dominant allele of MMR gene" are readable on unidentified nucleic acid sequences from mammals other than humans, which are yet to be identified at the time the invention was made, and which can be completely distinct from the exemplified *hPMS2-134* and those from the prior art. Applicant's disclosure of a truncated murine PMS2 and/or human PMS2, and/or potential biological assays to identify the sequences that exhibit a biological function as intended by the as-filed application, and/or potential techniques for making any claimed transgenic animal

including those of humans, does not provide sufficient description of the structures of a representative number of dominant negative MMR genes and/or transgenic animals, which would support applicant's possession of the genus of claimed DNA sequences coding for dominant negative MMR gene products, and/or of a generic transgenic clone at the time the invention was made. In other words, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims, *e.g.* genus animal dominant negative MMR genes including natural occuring MMR genes, and/or of a generic transgenic clone, requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays for isolating the variants; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of such claimed genus of any animal dominant negative MMR genes. A disclosure of no more than the *hPMS2-134* , as in the instant case, is simply a wish to know the identity of any or all DNA sequences encoding any naturally ocurring dominant negative PMS2 genes from any animal other than mouse and human, and of any transgenic clone whose genome containing a dominant negative MMR gene which must exhibit a particular hypermutable phenotype as intended by the as-filed application, *e.g.* the ability of the transgenic clone to produce altered polypeptides with enhanced antigenic and immunogenic activity and/or effective vaccines containing the altered polypeptides. The state of the art exemplified by Ngo *et al.* discloses that a nucleic acid sequence encoding a particular protein determines the protein' s structural, and functional properties, and a biological function of a encoded protein based on the primary amino acid sequence of the protein requires a knowledge of and description with regard to which amino acids in the protein' s sequence and/or nucleotides in the DNA, if any, are tolerant of modification and which are conserved (*i.e.,* expectedly intolerant to modification), and detailed knowledge of the ways in which a protein' s structure relates to its functional usefulness (Ngo *et al.,* in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.,* (ed.), Birkhauser, Boston, MA, pp. 492-495). In addition and with respect to claims readable on any transgenic clone, since differences in expression among lines of animals are caused by "position effect", and since host cell sequences at the site of integration can modify the regulation of the transgene both qualitatively and quantitatively, position effects where the transgene is influenced by its site of

integration in the host chromosome can have major consequences on the expression of the transgene, including loss of cell specificity, inappropriately high copy number-independent expression and complete silencing of the transgene (Polejaeva *et al.* (Theriogenology, Vol. 53, pages 117-126, 2000). More specifically, Polejaeva *et al.* states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

Thus, it is not apparent how one skilled in the art envisions a genus of "transgenic clone" that has no specific phenotype recited in the claims on the basis of applicant's specification. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Claiming all DNA and/or dominant negative MMR genes, and/or transgenic clones associated with any phenotype, which are broadly defined by the as-filed application, without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of the claimed DNA sequences and/or any phenotypic transgenic clones other than the truncated human or mouse PMS2, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Thus, it is not apparent to one skilled in the art as to how claims encompassing a genus "dominant negative

allele of MMR" genes and a genus of transgenic clones embraced by the claimed methods and products, find an adequate support from this instant disclosure at the time the invention was made.

Claims 1-4, 9-11, 22-25 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for claims limited to:

1/ A method for making a hypermutable, antibody producing cell *in vitro*, comprising introducing into an isolated cell capable of producing antibodies the *hPMS2-134* encoding polynucleotide, whereby said cell becomes hypermutable and is capable of producing antibodies;

2/ A homogenous culture of isolated hypermutable, antibody producing cells as described in 1/.

The specification is not enabling for claims directed to any other claimed embodiment within the elected claimed invention. The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description, particularly in view of the reasons set forth above, one skilled in the art would not known how to make and use the claimed invention as broadly claimed so that it would operate as intended by the disclosed as-filed application.

In addition, The specification coupled with knowledge in the prior art does not provide sufficient guidance and/or evidence for one skilled in the art to make and use the claimed invention readable on any transgenic clone, without any undue experimentation, particularly on the basis of applicant's disclosure.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

As the first issue, while the state of the art of transgenics is such that one skilled in the art can deliver and express a gene in a desired animal, it is not reasonably predictable for one skilled in the art to produce a transgenic animal that exhibit a desired phenotype, regardless whether a gene targeted modification technique rather than a traditional introduction of a desired exogenous protein encoded construct into embryonic cells. Applicants contemplates that by targeting any DNA vector construct encoding any dominant negative allele of MRR gene via homologous recombination into an endogenous genomic site containing the endogenous and native MMR gene of any animal cell including animal pluripotent, animal embryo-derived stem (ES) cells, an genetically modified transgenic clone and animal, for example, can be produced and can be employed to produce useful polypeptides as intended by the as-filed application. The specification provides no working examples showing a production and/or making of any transgenic animal having an intended phenotype, let alone any other phenotype as embraced by the claims. At the time the invention was made, the art of transgenics including gene targeted modification using ES cell technology was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells (Polejaeva *et al.* (Theriogenology, Vol. 53, pages 117-126, 2000). More specifically, Polejaeva *et al.* states:

> Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

Thus, it is not apparent as to how one skilled in the art, without any undue experimentation, makes and uses any transgenic animal which must exhibit a useful phenotype, particularly on the basis of applicant's disclosure.

Note that incorporation and expression of a human truncated human PMS2 encoded construct as a foreign genetic construct into any isolated cell for recombinant production of antibodies in a cell culture, does not necessarily mean a reasonable predictability of a phenotypic expression in the founder transgenic mouse whose genome contain the transfected human truncated PMS2 encoded gene. Furthermore, there is no evidence either from the specification or from the prior art that an correct introduction via homologous recombination of a truncated human PMS2 or mouse PMS2 gene into a mouse would generate any useful polypeptide for use as a vaccine as intended by the as-filed application. Thus, it is not apparent as to how one skilled in the art know how to make and/or use any transgenic animal including a claimed gene targeted transgenic mouse as embraced by the claims without undue experimentation.

To the extent that claims 1-4, and 9-11 are readable on a method of nucleic acid therapy comprising the step of administering to any target cell *in vivo* with any of the disclosed allelic dominant negative MMR gene, particularly in light of the specification, the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with it is most nearly connected, to make and/or use the invention.

The application and claims contemplate that any nucleic acid therapy method wherein any of the disclosed allelic dominant negative MMR gene is employed would generate a systemic hypermutation in

any animal so as to produce novel polypeptides that can be used as an immunognic or vaccine compositions . However, it is not apparent how one skilled in the art employs any of the disclosed allelic dominant negative MMR gene in any gene therapy method so as to generate applicant's intended objective. The application does not provide sufficient guidance and/or factual evidence for one skilled in the art to employ any of the disclosed allelic dominant negative MMR gene as nucleic acid therapeutic agents, without undue experimentation. Major considerations for any nucleic acid therapy protocol involve issues that include:

1/ The effect of an immune response against a gene therapy DNA before a therapeutic effect is generated;

2/ The type of vector and amount of DNA complexes to be administered;

3/ The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

4/ The fraction of vector taken up by the target cell population, the trafficking of the nucleic acid within cellular organelles, the rate of degradation of the nucleic acid, the level of mRNA produced, the stability of the nucleic acid product, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced; and

4/ What amount is considered to be therapeutically effective for a nucleic acid therapy method.

In addition, all of these issues differ dramatically based on the specific carrier used, the nucleic acid being used and the disease being treated.

Apart from the problems associated with the ability to import, package, transfect, so as to release a sufficient amount of therapeutic DNA inside the cytoplasm of a target cell as indicated in the preceding paragraphs, Anderson, Nature, Vol. 392, pp. 25-30, 1998, summarized the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer

and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). In addition, Verma *et al.,* Nature Vol. 389, pp. 239-242, 1997, states that out of the more than 200 clinical trials currently underway, no single outcome can be pointed to as a success story (page 239, column 1), and that one major obstacle to success has been the ability to deliver genes efficiently by non-viral vectors and obtain sustained expression (page 239, column 3). Even with *in vitro* cell culture trasnfected with the PMS2-134 truncated gene, Nicolaides *et al.* (Mole. Cellular Biology, Vol. 18, No. 3, p.1635-1641) teaches that (page 1640, column 2) the dominant negative attribute of the *hPMS2-134* mutant will only be manifest when it is present at sufficient concentration (at least equimolar)".

Given that *in vivo* nucleic acid therapy wherein any carrier including is employed to provide any intended effect other than simple gene expression in any and/or all mammals remains unpredictable at the tine the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any or all of the polynucleotide sequences cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention at its full breadth on the basis of applicant's disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in

the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-4, 9-11, 22-25 and 29 are rejected under 35 USC 102(b) by Nicolaides *et al.* (Molecular and Cell. Biology, Vol. 18, No.3, 1998), or in the alternative, under 35 USC 102(e) as being anticipated by US Pat No. 6,146,894 (where Vogelstein and Kinzler constitute as "an another").

With respect to the enabled claimed embodiment, Both Nicolaides *et al.*and the '894 patent teach a method of trasnfecting the *hPMS2-134* encoding polynucleotide into an isolated cell capable of producing antibodies (entire documents, also particularly claims 1 and 5, 7 and 9 of the '894 patent).

Absent evidence to the contrary, the transfected cell and cultures containing the trasnfected cells are capable of producing antibodies.

As a result of the disclosure and claim 1 and 5, 7 and 9 of the '894 patent where a distinct inventive entity is claimed, claims 1-4, 9-11, 22-25 and 29 are also rejected under 35 USC 102(f) because the applicant did not invent the claimed subject matter.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 9-11, 22-25 and 29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim of U.S. Patent No. 1 and 5, 7 and 9. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims embrace the same subject matter, namely a method of trasnfecting an isolated cell capable of producing antibodies the *hPMS2-134* encoding polynucleotide, wherein said trasfected cell is hypermutable and capable of producing antibodies.

No claims are allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER

A DOCPHOENIX

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REV 7/02/03